47. (New) The method according to claim 46, wherein IFN-γ is administered to a site of chronic wounding.

48. (New) The method according to claim 46, wherein between 7,500 and 15,000 IU of IFN-γ is administered.

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49. (New) The method according to claim 46, wherein IFN-γ is administered in combination with a pharmaceutically acceptable carrier, diluent or excipient.

REMARKS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

Claims 39-43 have been cancelled and new claims 46 to 49 have been added. New claim 46 corresponds to prior claim 39 except that claim 46 refers to IFN-γ *per se*, as opposed to "a stimulator of IFN-γ". New claim 47 corresponds to prior claim 40, but specifies that the site of wounding is a site of *chronic* wounding. New claim 48 corresponds to prior claim 41. New claim 49 corresponds to prior claim 43 but specifies IFN-γ *per se*, as opposed to "a stimulator of IFN-γ". Given the nature of the amendments made, no replacement of prior claim 42 is presented. That

the claims have been revised should not be taken as an indication that Applicant agrees with any view expressed by the Examiner. Rather, the revisions are offered merely to advance prosecution and Applicant reserves the right to pursue any deleted subject matter in a continuation application.

Claims 40-42 stand rejected under 35 USC 112, second paragraph, as allegedly being indefinite. Withdrawal of the rejection is submitted to be in order in view of the above-noted claim revisions and further in view of the comments that follow.

New claim 46, from which the remaining claims depend, recites interferon-γ *per se*, as opposed to "stimulators of interferon-γ". This revision addresses the point raised by the Examiner in connection with claim 41.

New claim 47 recites "a site of chronic wounding", thereby mooting the Examiner's concern as regards now cancelled claim 40.

The language to which the Examiner objects in connection with now cancelled claim 42 does not appear in the newly presented claims.

In view of the above, reconsideration is requested.

Claims 39 to 43 stand rejected as allegedly being non-enabled. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

The rejection appears to be based on a perceived discrepancy between the use of anti-interferon-γ to prevent scarring described in the earlier part of the specification, and the use of interferon-γ to promote healing of chronic wounds, described in the later part of the specification. Applicant respectfully submits that the two uses described are not in fact contradictory, for the reasons set out below.

The person skilled in the art would appreciate that the wound healing response is "classically" considered to result from the interplay of a number of processes or phases:

i) the inflammatory response;

ii) granulation tissue formation and angiogenesis;

iii) wound contraction; and

iv) remodelling of the resultant scar.

It is the first and second phases (in which granulation tissue is formed, collagen deposited and blood supply to the damaged area restored - under the influence of factors released by cells of the inflammatory response) that provide the material that fill the wound defect.

Differing magnitudes of the fibrotic response (granulation tissue formation, angiogenesis and collagen deposition) can cause different outcomes of healing. Extremes of the response can result in different forms of pathological healing.

It is recognized that over-exuberant fibrosis leads to prominent scar formation. In such cases, the wound defect is rapidly re-filled but the quality of the resultant scar is poor. It is in this context that the use of anti-interferon-γ therapy, to reduce granulation tissue deposition and hence eventual scarring, is contemplated.

The present application, however, is directed to the opposite situation - that of chronic wounds. As described in the passage spanning pages 1 and 2 of the instant specification, such wounds are characterized by a retarded, or non-existent, healing response causing production of a non-healing wound or ulcer.

Chronic wounds result from a deficient fibrotic response. As such they lack cells and extracellular matrix to fill the wound defect. Indeed, the presence in a chronic wound of granulation tissue (which provides an indication of the fibrotic response) is recognized as an indication that the wound is beginning to heal in a "normal" fashion. The importance of granulation tissue

formation (and hence fibrosis) as a sign of healing is recognized in a number of published scales for assessment of chronic wound healing, as summarized below:

(i) "OASIS"

According to a first published scale, the status of a pressure ulcer may be described using "OASIS" (Outcome and Assessement Information Set) terminology. The terms were formulated to guide reimbursement of care, and are based on a WOCN (Wound Ostomy Continence Nurse Society) Guidance document. Using the OASIS terminology the presence of granulation tissue (a component of the fibrotic response) in the chronic wound bed is taken as indicative of healing of the wound.

(ii) "PUSH"

The Pressure Ulcer Scale for Healing (PUSH) represents a second scale for evaluating pressure ulceration. This scale can be used to monitor the status of the ulcer over time and its response to clinical intervention. The scale was developed by the PUSH Task Force and sponsored by the National Pressure Ulcer Advisory Panel. As part of a total assessment under the PUSH scale, the presence of granulation tissue in the ulcer attracts a score of 2 out

of 4 (where 0 represents a healed ulcer and 4 a non-healing ulcer containing necrotic tissue).

As illustrated by the above comments, the skilled person would, at the filing date of the application, have recognized that an agent capable increasing fibrosis, i.e., increaseing inflammation and collagen deposition, would have utility in promoting the healing of chronic wounds (while concomitantly increasing the degree of scarring).

Thus, the skilled person would perceive that the ability of interferon-γ to increase inflammation and angiogenesis in 7 day and 14 day wounds (as described in the results reported at page 9 of the specification) indicates that interferon-γ is able to increase the strength of the wound healing response, and thereby promote healing of chronic wounds.

Similarly, the skilled person would recognize that the increased scarring, described in 70 and 120 day wounds that had been treated with interferon-γ, is a consequence of the same increase in the wound healing response, the like of which it is desired to induce in chronic wounds.

Finally, the skilled person would appreciate that the dose-dependent increase in collagen present in interferon-γ treated wounds would be beneficial in inducing healing of

chronic wounds, which otherwise suffer from reduced extracellular matrix deposition.

The Examiner refers to the factors, set out in *"Wands"*, which should be considered in determining whether a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue". These factors are discussed below:

1. The nature of the invention.

The present invention, that is to say, methods suitable for promotion of healing of chronic wounds, lies in a field of the art in which a certain degree of experimentation (such as pilot studies, clinical trials etc.) is necessary in order to meet statutory regulations. This requirement should be considered as a mitigating factor when assessing what constitutes an unnecessary burden of experimentation.

2. The state of the prior art.

As described above, at the priority date of the instant application there existed a wealth of information available to the skilled person to illustrate that increasing the magnitude of the wound healing response (and thus fibrosis indicated by granulation tissue formation)

was a positive indicator of healing in chronic wounds. The skilled person would therefore have immediately appreciated that the results described in the instant application, which illustrate that treatment with exogenous interferon-γ causes an increase in inflammation, angiogenesis and collagen deposition, indicate that interferon-γ is likely to have utility in promoting healing of chronic wounds.

3. The relative skill of those in the art.

The skilled person in the field of wound healing research is typically of post-doctoral level qualification. Such a skilled person would immediately recognize that compounds capable of increasing scarring and fibrosis (by increasing inflammation, angiogenesis and extracellular matrix deposition) demonstrate properties that would make them suitable candidates for treatment of chronic wounds - conditions that are characterized by reduced fibrosis and matrix formation.

4. The level of predictability in the art.

Those involved in research leading to the production of novel clinical therapies are familiar with the need to extrapolate results gained from animal experiments to a human clinical context. The field of wound healing, by its

very nature, is one in which animal models are used extensively, due to ethical constraints which prevent large-scale experimental wounding of human subjects. Although not all treatments that are effective in animal models are ultimately suitable for use in human patients, it is widely accepted that treatments that are efficacious in animal models represent promising subject matter.

In this context the skilled person would immediately appreciate that interferon-γ's ability to induce inflammation, angiogenesis and extracellular matrix deposition to increase fibrosis in animal models of wound healing identifies it as a compound likely to be useful in the context of promoting healing of chronic wounds in humans.

5. The existence of working examples.

The replacement claims submitted with this response have been amended such that they relate only to interferon-γ *per se*, rather than "stimulators of interferon-γ" as previously claimed. The instant specification provides, in the experimental results section, clear description of treatment with exogenous interferon-γ, both prior to and after wounding.

In experimental group C, animals were treated with either 15,000 or 7,500 IU of interferon-γ, administered via intradermal injection, prior to wounding. In experimental group D, animals were treated with the same amount of interferon-γ, administered by the same route, both before and after wounding. Thus the instant specification contains working examples describing use of exogenous interferon-γ, both for treatment of existing wounds and prophylactic treatment at a site to be wounded.

Animals of both experimental group C and experimental group D exhibited the same dose dependent effects in response to interferon-γ treatment. These effects were to increase inflammation and angiogenesis in day 7 and day 14 wounds, and to promote greater fibrosis in day 70 and day 120 wounds.

The skilled person would readily appreciate that the ability of exogenous interferon-γ to increase inflammation, angiogenesis and collagen deposition indicates that interferon-γ may be used to promote the healing of chronic wounds in which these responses are normally deficient.

6. The breadth of the claims.

As noted above, the claims submitted with this response relate only to interferon-γ *per se*. The results

reported in the specification of the instant application describe the use of interferon-γ in animal models of wound healing to increase inflammation, angiogenesis and collagen deposition, and hence increase fibrosis. Such increased fibrosis is beneficial in promoting the healing of chronic wounds.

In reciting interferon-γ *per se*, the current claims are entirely commensurate in scope with the disclosure provided.

7. The amount of direction or guidance provided by the inventor.

The instant application provides detailed guidance as to:

i) suitable routes of administration of interferon-γ to promote wound healing (e.g., by intradermal injection);

ii) suitable times at which interferon-γ can be administered to promote wound healing (e.g., before wounding or after wounding, at the site of an existing wound); and

iii) suitable amounts of interferon-γ that can be used to promote wound healing (e.g., 15,000 or 7,5000 IU).

The specification thus provides ample direction and guidance to allow the skilled person to put the invention into practice.

8. The quantity of experimentation needed to make or use the invention.

The instant application discloses the use of interferon-γ to promote wound healing in an animal model by inducing increased granulation tissue formation and extracellular matrix deposition.

Determining the precise quantities of an experimental agent that are necessary to achieve the desired clinical effect in a human context is a necessary part of all work aimed at providing clinically acceptable therapies or prophylactic treatments. Thus the skilled person would accept that the limited experimentation necessary to extrapolate the results described from their context in an animal model to their use in human therapies in no way represents an unnecessary burden.

In view of the above, reconsideration is requested.

Claims 39, 40 and 43 stand rejected under 35 USC 112, first paragraph, as allegedly lacking written description. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

New claims 46 to 49 make reference to interferon-γ *per se* to promote healing of chronic wounds. Since the source, quantity and use of interferon-γ are clearly described in the experimental section of the instant application, it is apparent Applicant was indeed in possession of the subject matter now claimed.

Reconsideration is requested.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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